

REVIEW ARTICLE

Trauma

Appraising the use of tranexamic acid in traumatic and non-traumatic intracranial hemorrhage: A narrative review

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Abstract

Recently there has been increasing interest and debate on the use of tranexamic acid (TXA), an antifibrinolytic drug, in both traumatic and non-traumatic intracranial hemorrhage. In this review we aim to discuss recent investigations looking at TXA in traumatic brain injury (TBI) and different categories of spontaneous intracranial hemorrhage. We also discuss differences between setting (hospital vs pre-hospital), dosing and timing strategies, and other logistical challenges surrounding optimal use of TXA for isolated intracranial hemorrhage. Last, we hope to provide guidance for clinicians when considering the use of TXA in a patient with traumatic or non-traumatic intracranial hemorrhage based on appraisal of the available literature as well as some potential ideas for future research in this area.

1 | INTRODUCTION

Intracranial hemorrhage encompasses any bleeding in the brain tissue (ie, intraventricular and intraparenchymal) or the areas between the skull and brain tissue (ie, epidural hematoma, subdural hematoma, subarachnoid hemorrhage [SAH]), whereas intracerebral hemorrhage (ICH) refers to bleeding that occurs only within the brain tissue. Although the pathophysiology of spontaneous and traumatic intracranial hemorrhage is substantially different, efforts to control and minimize hematoma or hemorrhage size in both conditions have important implications in terms of patient outcome.^{1–3}

Excessive fibrinolysis, or hyperfibrinolysis, has been identified in patients with spontaneous and traumatic intracranial hemorrhage and may represent an approach to limit hematoma expansion and improve patient outcomes.^{1–3} Fibrinolysis can briefly be described as a normal physiological process mediated through activation of plasminogen

designed to counterbalance clot formation.⁴ In hyperfibrinolysis, excessive breakdown of hemostatic plugs can lead to rebleeding and hematoma expansion. The incidence of hematoma expansion in patients with intracranial hemorrhage secondary to traumatic brain injury (TBI) are variable with a range of 11.3% to 51% depending on timing of repeat computed tomography (CT) of the head, severity of injury, and bleed location.^{5–8} Similarly, the incidence of hematoma expansion after spontaneous ICH varies widely, ranging from 13% to 38%.⁹ Although other mechanisms for hematoma expansion have been reported, hyperfibrinolysis is commonly reported in patients with intracranial hemorrhage with rates of up to 37%.¹⁰ The incidence of fibrinolysis in spontaneous ICH is poorly described; however, laboratory evidence of fibrinolysis is frequently identified particularly in patients with delayed cerebral ischemic events.^{11–13}

Tranexamic acid (TXA) is an antifibrinolytic agent that exerts its mechanism of action via antagonism of lysine binding sites on plasminogen thus preventing its interaction with fibrin,¹⁴ thus inhibiting dissolution and degradation of fibrin clots by plasmin that shifts the

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balance toward clot stabilization.^{15,16} The use of TXA in surgical patients has been extensively studied and has been shown to reduce blood transfusion requirements; however, investigations of the effects on other outcomes such as mortality and need for reoperation because of bleeding have reported variable results.^{17,18} The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH)-2 trial was the first large-scale, randomized controlled study to demonstrate a reduction in death from bleeding in TXA-treated trauma patients with suspected hemorrhage.¹⁹ Since CRASH-2, several trials have been conducted to further elucidate the effect of TXA on clinical outcomes related to those with suspected or confirmed intracranial hemorrhage secondary to TBI²⁰⁻²² as well as other non-traumatic forms of intracranial bleeding such as spontaneous ICH and SAH.²³⁻²⁶ The aim of this narrative review is to evaluate the efficacy and safety of TXA in traumatic and spontaneous intracranial head injuries as well as discuss several considerations with its use in these settings. This will hopefully serve as a resource for clinicians and provide guidance for decision-making processes regarding TXA administration for patients presenting with head-related bleeding.

2 | TXA USE IN TBI

The progression of TBI is a complex process that can be broken down into primary and secondary injuries, the latter of which is attributed to molecular, chemical, and inflammatory cascades responsible for further neuronal damage that may occur hours to days after the initial injury.²⁷ Therefore, the role of TXA is more relevant in the early stages of TBI to help reduce or prevent intracranial bleeding and subsequent negative sequelae.

The CRASH-2 trial reported that TXA significantly decreased all-cause, 28-day, in-hospital mortality (14.5% vs 16%; RR, 0.91; 95% confidence interval [CI], 0.85–0.97; $P = 0.0035$) and death attributed to bleeding (4.9% vs 5.7%; relative risk [RR], 0.91; 95% CI, 0.76–0.96; $P = 0.0077$) in trauma patients.¹⁹ The benefits of TXA on reducing the risk of death from bleeding were most pronounced when administered within the first hour of injury (5.3% for TXA vs 7.7% for placebo; RR, 0.68; 95% CI, 0.57–0.82; $P < 0.0001$), whereas treatment given after 3 hours was associated with an increased risk of death from bleeding (4.4% for TXA vs 3.1%; RR, 1.44; 95% CI, 1.12–1.84; $P = 0.004$).²⁸ In a prespecified subgroup analysis, there were no significant mortality differences between groups based on initial Glasgow Coma Scale (GCS) scores at randomization, although it is unclear how many patients in each subgroup had intracranial bleeding or TBI versus other causes of altered mental status (eg, shock, medications, and illicit drugs).²⁸ A nested randomized controlled trial within CRASH-2 including 270 patients with CT-confirmed TBI found that TXA was associated with a non-significant reduction in both total hemorrhage growth and a decreased rate of new intracranial hemorrhage development.²⁹ Despite the small sample size, the authors acknowledged that these results could not exclude moderate benefits nor harmful effects of TXA in patients with TBI given the low incidence of new focal cerebral ischemic lesions in both groups.

A group of investigators in Thailand conducted a randomized controlled trial in 238 patients with moderate to severe TBI either in isolation or with concomitant polytrauma.³⁰ In patients with moderate to severe TBI, TXA did not significantly reduce progressive intracranial hemorrhage compared with placebo, which was defined as a new intracranial hemorrhage or increase in size by $\geq 25\%$ from initial to repeat CT scan. Of note, the average time from injury onset to enrollment in this trial was approximately 7 hours, which exceeds the purported time window of benefit of 3 hours based on findings from previous investigations of TXA.^{19,28,29,31} A meta-analysis by Weng et al that included data from the Thailand study³⁰ reported that TXA administration was associated with a significant reduction in total ICH growth,³² which was primarily driven by a separate study that enrolled patients < 3 hours from initial injury.³³ Despite data suggesting that there could be a beneficial effect of TXA reducing ICH expansion in patients with TBI, individual trials up until the publication of the meta-analysis by Weng et al were limited by small sample size and inclusion of heterogeneous populations of patients with extracranial injuries in addition to the presence of TBI.

The CRASH-3 study was a multinational, randomized controlled trial designed to evaluate the efficacy of TXA compared with placebo in reducing head injury-related death in patients with isolated TBI (any CT-confirmed ICH without major extracranial bleeding or GCS score of ≤ 12).³⁴ There was no difference in the primary outcome of head injury-related death in hospital within 28 days of injury between those allocated to receive TXA versus placebo within 3 hours of injury (18.5% vs 19.8%; RR, 0.94; 95% CI, 0.86–1.02), even after excluding patients with a GCS score of 3 or bilateral unreactive pupils (12.5% vs 14.0%; RR, 0.89; 95% CI, 0.8–1.0). An a priori subgroup analyses indicated that TXA led to a statistically significant reduction in head injury-related deaths in those with mild to moderate TBI (GCS 9–15), whereas there were no differences noted in those with severe TBI (GCS 3–8) regardless of how early treatment was initiated. Despite not being supported by the primary analysis, the investigators concluded that TXA treatment within 3 hours of injury reduced head injury-related deaths. The message of this trial should be interpreted with caution as TXA did not reduce mortality in the overall cohort, and it was only in a subgroup analysis of patients with mild-moderate TBI, and even then, the possibility of a type 1 error accounting for this difference cannot be excluded. With respect to adverse effects, there was a similar incidence of vascular occlusive events and seizures in the TXA and placebo groups in this study, thus suggesting that TXA is relatively safe to use.

There have been several meta-analyses that have combined the results of CRASH-3 with previously discussed TXA trials, with one suggesting clinical benefits with TXA³⁵ and others finding no statistically significant differences in any clinical outcomes.^{36,37} The reasons for these differences are multifaceted; however, some of the key elements to consider when examining these pooled analyses include variation of inclusion criteria (eg, patients with polytrauma vs isolated TBI only), imbalances or incomplete reporting regarding baseline TBI severity, inclusion of studies with high versus low risk of bias, and differences in analytical methods (eg, using a fixed- vs random-effects model and

sensitivity analyses). In addition, the inability to complete specific subgroup analyses of patients who may benefit (eg, patients with mild to moderate TBI) from TXA in these meta-analyses make it difficult to exclude the possibility of improved outcomes in certain patient populations with TBI.

3 | PREHOSPITAL USE OF TXA IN PATIENTS WITH TBI

Given the promising effects of TXA when administered closer to the time of injury,^{19,20,31} it seems logical to hypothesize that prehospital administration of TXA may confer improved clinical outcomes. Two subsequent trials to the CRASH investigations examined the role of prehospital administration of TXA in patients with TBI, one large retrospective cohort study²¹ and the other a prospective randomized controlled study.²²

Bossers et al performed a retrospective analysis of prospectively collected information from the Brain Injury: Prehospital Registry of Outcome, Treatments, and Epidemiology of Cerebral Trauma (BRAIN-PROTECT) database.²¹ Patients with suspected severe TBI based on trauma mechanism and GCS score of ≤ 8 who were transported to 1 of 9 participating trauma centers were included in the analysis. Patients with extracranial trauma were included in the analysis, and planned subgroup analyses of patients with confirmed severe TBI and isolated TBI were stated a priori. The dose of TXA was not standardized; however, most patients received a dose of 1 g (90% of patients). Patients with isolated severe TBI who received any TXA in the prehospital setting had higher mortality rates compared with patients who did not receive TXA after adjustment for potential confounders (odds ratio [OR], 2.05; 95% CI, 1.22–3.45; $P = 0.007$).²¹ No differences in mortality after adjustment for potential confounders were noted between those receiving or not receiving TXA in the overall cohort nor in those with confirmed severe TBI. Although it was not feasible to obtain a CT-confirmed diagnosis of TBI in the prehospital setting, a limitation of this investigation was enrollment based primarily on GCS, which can be affected by factors not specific to TBI, such as hypoxia, hypotension, and prescription or illicit drug use. In addition, allocation bias may have preferentially given those with a more severe presentation a higher likelihood of receiving TXA, which may be a factor affecting the outcomes in this study.

Rowell et al performed a prospective, randomized controlled trial assessing prehospital administration of TXA in patients aged 15 years or older with moderate to severe TBI, a GCS score of ≤ 12 , at least 1 reactive pupil, and a systolic blood pressure ≥ 90 mmHg.²² Participants were randomly assigned to receive either a 1 g bolus plus an infusion of 1 g over 8 hours, a 2 g bolus plus placebo infusion, or placebo bolus and infusion within 2 hours of injury. All boluses regardless of treatment allocation were administered before hospital arrival via emergency medical services personnel. There were no significant differences in the primary outcome of favorable 6-month neurologic outcomes nor secondary outcomes of 28-day mortality between the combined TXA and placebo groups (14% vs 17%; $P = 0.26$).²² There are some impor-

tant considerations regarding the patients and methods between this study and CRASH-3. Overall mortality was slightly lower but similar in this investigation compared with that in CRASH-3 ($\approx 19\%$ overall mortality)^{21,22,34} despite there being a higher proportion of patients with severe TBI in the study by Rowell et al (GCS ≥ 12 at baseline 3% vs 28%, respectively). In addition, only 58% of patients in the Rowell et al trial had CT-confirmed intracranial hemorrhage on hospital admission, whereas this was not explicitly reported in the CRASH-3 trial. Thus, a considerable proportion of patients would likely have not benefited from TXA administration in the absence of intracranial bleeding. This underscores 1 of the many constraints of prehospital research, wherein clinical diagnosis at randomization (in the field) may change on admission to the hospital. Another notable finding from this study was that a higher proportion of individuals experienced witnessed seizures or seizure-like activity in the TXA bolus-only group compared with the bolus-maintenance and placebo groups (5% vs 2% vs 2%). Interestingly, the adjusted difference in seizures was statistically significant between the bolus-only and bolus-maintenance group, and this finding deserves further consideration. Although there has been ongoing debate about the prehospital administration of TXA in those with TBI,³⁸ the results from this study do not currently support its routine administration in those with isolated moderate–severe TBI. Table 1 summarizes the key clinical trials that examined TXA use in patients with TBI.

4 | TXA USE IN SPONTANEOUS ICH

Management of patients with spontaneous ICH has largely focused on minimizing hematoma expansion, which is associated with neurologic deterioration and poor patient outcomes.³⁹ Current guidelines recommend early intensive blood pressure lowering to a systolic blood pressure < 140 mmHg to limit hematoma expansion and potentially improve functional neurological outcomes based on the results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)-2 study.^{40–42} Observational trials of rapid administration of TXA in addition to blood pressure control demonstrated benefits decreasing hematoma enlargement; however, prospective trials were limited until recently.^{43,44} Renewed interest in the use of early, short-course TXA became more prevalent after the positive results of other studies demonstrating benefit in specific cohorts or subgroups of patients with non-surgical bleeding.^{19,20}

Early prospective, randomized controlled trials were underpowered to evaluate clinically important outcomes, so the focus was often on hematoma expansion. Arumugam et al performed a single-blinded, randomized controlled trial comparing hematoma growth in patients with acute ICH within 8 hours of symptom onset treated with either TXA or placebo.⁴⁵ No differences in hematoma growth were reported in the TXA group (10.64 mL at baseline vs 10.94 mL at 24 hours; $P = 0.313$), whereas the placebo group experienced an increase in hematoma volume. The Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage (TICH) trial, designed as a pilot study to test the feasibility of performing the larger TICH-2 clinical trial, was a double-blind, randomized controlled study comparing adult

TABLE 1 Summary of select trials on short-course tranexamic acid in traumatic and non-traumatic head injuries and bleeding

Trial	Population	TXA regimen	Outcomes	Comments
Traumatic brain injury				
Perel et al, 2012 ²⁹ ; CRASH-2 ICH	CRASH-2 participants with GCS ≤ 14 and head CT compatible with TBI TXA, n = 133 Placebo, n = 137	1 g IV bolus over 10 minutes followed by 1 g IV over 8 hours	<ul style="list-style-type: none"> Non-significant reduction in hemorrhage growth in TXA-treated patients (-3.8 mL; 95% CI, -11.5 to 3.9 mL) No difference in mortality (aOR, 0.49; 95% CI, 0.22-1.06) No difference in need for neurosurgical intervention (aOR, 0.98; 95% CI, 0.5-1.91) 	<ul style="list-style-type: none"> Subgroup cohort Not powered to detect differences in clinical outcomes with those presenting with TBI
Yutthakemsunt et al, 2013 ³⁰	Patients aged 16 years and older with GCS 4-12 with head CT within 8 hours of injury, no immediate surgical intervention TXA, n = 120 Placebo, n = 120	1 g IV bolus over 30 minutes followed by 1 g IV over 8 hours	<ul style="list-style-type: none"> No difference in progressive intracranial hemorrhage growth (RR, 0.65; 95% CI, 0.4-1.05) No difference in mortality (RR, 0.69; 95% CI, 0.35-1.39) No difference in adverse events 	<ul style="list-style-type: none"> Most patients received treatment > 7 hours from injury
CRASH-3 Trial Collaborators, 2019 ³⁴	Adults with GCS ≤ 12 and head CT confirmed bleeding, presenting within 8 hours of injury (later amended to 3 hours) TXA, n = 4613 Placebo, n = 4514	1 g IV bolus over 10 minutes followed by 1 g IV over 8 hours	<ul style="list-style-type: none"> No difference in head injury-related death at 28 days, except in those with GCS 9-15 (RR, 0.78; 95% CI, 0.64-0.95) No difference in patient-derived disability measures for survivors No difference in vascular occlusive events or seizures 	<ul style="list-style-type: none"> Overall conclusion not supported by statistical findings Grouped mild and moderate TBI (GCS 9-15) together, which limits more stringent subgroup comparisons
Rowell et al, 2020 ²²	Patients aged 15 years and older with GCS 3-12, at least 1 reactive pupil, and SBP ≥ 90 mmHg in prehospital setting within 2 hours of injury TXA, n = 657 Placebo, n = 309	1 g IV bolus prehospital followed by 1 g IV over 8 hours in hospital (n = 312) 2 g IV bolus prehospital followed by placebo infusion over 8 hours in hospital (n = 345)	<ul style="list-style-type: none"> No difference in clinical outcomes between combined TXA group and placebo More occlusive events and seizures/seizure-like activity in the bolus-only group compared with the bolus-maintenance and placebo groups (5% vs 2%, respectively) 	<ul style="list-style-type: none"> Of the patients, 20% had GCS > 12 at hospital arrival (possible recovery from mild injury vs effects of drugs or illicit substances) Difficult to accurately assess TBI severity in prehospital setting without CT scan Only 12% patients had evidence of hyperfibrinolysis, unclear if presence of this coagulopathy confers benefit (subgroup analysis not done)

(Continues)

TABLE 1 (Continued)

Trial	Population	TXA regimen	Outcomes	Comments
Spontaneous intracerebral hemorrhage				
Striggle et al, 2014 ⁴⁶ ; TICH-1 trial	Adult patients with spontaneous ICH enrolled within 24 hours of onset at a single institution TXA, n = 16 Placebo, n = 8	1 g infusion over 10 minutes followed by 1 g infusion over 8 hours	<ul style="list-style-type: none"> Adverse events reported in 6 patients treated with TXA and 2 patients treated with placebo. Of 8 adverse events reported, 7 were related to neurologic deterioration No differences in neurologic outcomes, health-related quality of life measures, length of hospital stays, or patient disposition at 90 days 	<ul style="list-style-type: none"> Feasibility trial for the larger TICH-2 trial
Arumugam et al, 2015 ⁴⁵	Patients aged 18 years and older with hypertensive ICH within 8 hours of onset deemed to be non-surgical candidates at a single institution TXA, n = 15 Placebo, n = 15	1 g infusion over 10 minutes followed by 1 g infusion over 8 hours	<ul style="list-style-type: none"> Change in hematoma volume in TXA group between initial and repeat head CT at 24 hours not significant (median change in volume, 0.212 mL; $P = 0.313$) Change in hematoma volume in placebo group between initial and repeat head CT significantly higher (median change in volume, 3.07 mL; $P = 0.0001$) 	<ul style="list-style-type: none"> Blood pressure controlled with labetalol infusion to maintain SBP 140–160 mmHg
Spriggle et al, 2018 ⁴⁷ ; TICH-2 trial	Adult patients with acute ICH within 8 hours of symptom onset TXA, n = 1161 Placebo, n = 1164	1 g bolus over 10 minutes followed by 1 g infusion over 8 hours	<ul style="list-style-type: none"> No differences in neurologic outcome as evaluated by the mRS at 90 days between patients who received TXA and placebo (ordinal OR, 0.88; 95% CI 0.76–1.03; $P = 0.11$) Lower mortality at 7 days in the TXA group compared to placebo (9% vs 11%; binary OR, 0.73; 95% CI 0.53–0.99; $P = 0.0406$) Hematoma expansion at 24 hours was significantly lower in the TXA group compared with placebo (25% vs 29%; aOR, 0.80; 95% CI, 0.66–0.98; $P = 0.03$) No differences in death at 90 days ($P = 0.37$), hospital length of stay ($P = 0.16$), or health-related quality of life measures Serious adverse events were lower in the TXA group compared with placebo at day 2 ($P = 0.0272$), day 7 ($P = 0.02$), and day 90 ($P = 0.0393$). Seizures and thromboembolic events were similar between groups 	<ul style="list-style-type: none"> Overall difference in hematoma volume between TXA and placebo groups was 1.37 mL Post hoc analysis of patients with hematoma volumes between 30 and 60 mL had better neurologic outcomes in the TXA group compared with placebo Of the patients, >64% were randomly assigned between 3 and 8 hours after stroke onset

(Continues)

TABLE 1 (Continued)

Trial	Population	TXA regimen	Outcomes	Comments
Meretoja et al, 2020 ⁴⁹ ; STOP-AUST trial	Patients aged 18 years or older with ICH meeting prespecified clinical criteria (eg, GCS > 7, ICH volume < 70 mL) and contrast extravasation on CT angiogram (positive spot sign) within 4.5 hours of symptom onset TXA, n = 50 Placebo, n = 50	1 g bolus over 10 minutes followed by 1 g infusion over 8 hours	<ul style="list-style-type: none"> Intracerebral hematoma growth, defined as at least a 33% or 6 mL absolute increase from baseline to 24 hours, was similar in patients who received TXA and placebo (44% vs 52%; effect size, 0.72; 95% CI, 0.32–1.59; $P = 0.41$) No differences in secondary outcomes including mRS score at 90 days ($P = 0.97$), absolute ICH growth ($P = 0.28$), absolute intraventricular hemorrhage growth ($P = 0.99$), and death at 90 days ($P = 0.19$) Thromboembolic events were similar between groups ($P = 0.57$) 	<ul style="list-style-type: none"> The study took > 6 years to enroll 100 patients at 13 stroke centers; of the 7 centers reporting exclusion criteria, 3325 patients with ICH were admitted, with 88 (2.6%) enrolled in the study
Liuet al, 2021 ⁵⁰ ; TRAIAGE trial	Patients between the ages of 18 and 70 years with ICH, symptom onset within 6 hours, and indications of a high risk for hematoma expansion either on CT angiography (ie, spot sign) or non-contrast CT (ie, blend or black hole sign) TXA, n = 89 Placebo, n = 82	1 g bolus over 10 minutes followed by 1 g infusion over 8 hours	<ul style="list-style-type: none"> Incidence of hematoma expansion, defined as an increase in hematoma volume > 33% or absolute increase of > 6 mL from baseline to 24 hours, was similar between patients who received TXA and placebo (40.4% vs 41.5%; OR, 0.96; 95% CI, 0.52–1.77; $P = 0.89$) Secondary endpoints including mRS score, death at 90 days, ICH growth volume, and major thromboembolic events were similar between groups 	<ul style="list-style-type: none"> Study was terminated before target enrollment of 188 patients after publication of the STOP-AUST trial demonstrating no effect of TXA on hematoma expansion in a similar patient population
Aneurysmal SAH				
Hillman et al, 2002 ⁵⁷	Patients at least 15 years of age with SAH confirmed with CT within 48 hours of hospital admission were enrolled; randomized treatment was later discontinued in patients without evidence of aneurysm TXA, n = 254 Control, n = 251	1 g infusion before transport to regional neurosurgical center followed by 1 g infusion 2 hours after the initial dose. Treatment with TXA 1 g every 6 hours was continued until the aneurysm was occluded or for up to 72 hours	<ul style="list-style-type: none"> Early rebleeding based on repeat head CT was less common in the TXA group compared with control (2.4% vs 10.8%; $P < 0.01$) Rates of permanent stroke related to delayed ischemic events were similar between the TXA group and control (3.9% vs 4.8%; ns) No differences in favorable Glasgow Outcome Scale scores between the TXA group and placebo (74.8% vs 70.5%; ns) No statistical differences in the rate of death between the TXA group and control (12.9% vs 16.3%) 	<ul style="list-style-type: none"> Interpretation of rebleeding rates complicated because clinical progress determined the need for repeat CT scans Aneurysms were clipped or coiled within 24 hours in 70% of patients

(Continues)

TABLE 1 (Continued)

Trial	Population	TXA regimen	Outcomes	Comments
Post et al, 2021 ⁵⁸ ; ULTRA trial	Adult patients aged 18 years or older with non-contrast CT confirming SAH and within 24 hours of SAH symptom onset and GCS <13. TXA, n = 480 Control, n = 475	1 g bolus followed by 1 g infusion every 8 hours until endovascular or surgical intervention of the aneurysm or until a maximum of 24-hour treatment with a total maximum TXA dose of 4 g	<ul style="list-style-type: none"> The incidence of positive neurologic outcome at 6 months, defined as an mRS score of 0–3, was similar between the TXA and control groups (60% vs 64%; OR, 0.87; 95% CI, 0.67–1.13) Incidence of excellent neurologic outcome, defined as an mRS score of 0–2, was lower in the TXA group compared with control (OR, 0.74; 95% CI, 0.57–0.96) The TXA and control groups had similar mortality rates at 30 days (22% vs 22%; OR, 0.98; 95% CI, 0.72–1.33) and 6 months (27% vs 24%; OR, 1.15; 95% CI, 0.86–1.54) There were no differences in the incidence of adverse effects, including rebleeding, delayed cerebral ischemia, and thromboembolic complications 	<ul style="list-style-type: none"> Median time from symptom onset and initiations of TXA was 3 hours Median time from diagnosis to aneurysm treatment was 14 hours

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CRASH, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; CT, computed tomography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; ns, not significant; OR, odds ratio; RR, relative risk; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; STOP-AUST, Spot Sign and Tranexamic Acid on Preventing ICH Growth-AUSTRALASIA study; TBI, traumatic brain injury; TICH, Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage; TRAIGE, Tranexamic Acid for Acute Intracerebral Haemorrhage Growth Based on Imaging Assessment; TXA, tranexamic acid; ULTRA, Ultra-Early Tranexamic Acid After Subarachnoid Haemorrhage.

patients with acute spontaneous ICH within 24 hours of symptom onset treated with either TXA or placebo.⁴⁶ A non-significant difference in hematoma expansion was reported in 18.8% of patients in the TXA group and 12.5% of patients in the placebo group with a similar incidence of serious adverse events.

The TICH-2 trial was a double-blind, placebo-controlled, phase 3 trial of adult patients with spontaneous ICH within 8 hours of symptom onset at 124 hospitals in 12 countries.⁴⁷ All patients received standard care consisting of blood pressure-lowering treatment, neurosurgical procedures, and venous thromboembolism prophylaxis according to published clinical guidelines. There were no significant differences in functional outcome at day 90 as assessed by the modified Rankin Scale (mRS) between the TXA and placebo groups (ordinal OR, 0.88; 95% CI, 0.76–1.03; $P = 0.11$). Changes in hematoma volume from baseline to 24 hours were smaller in the TXA group compared with placebo as was the incidence of hematoma expansion. Death at day 7 was also lower in the TXA group; however, 90-day mortality was similar. Prespecified subgroup analysis indicated that patients with a mean systolic blood pressure ≤ 170 mmHg who received TXA had better functional outcomes at day 90 compared with placebo (OR, 0.73; 95% CI, 0.59–0.9). Similarly, a post hoc analysis suggested that patients with a baseline hematoma volume between 30 and 60 mL who received TXA had better functional outcomes at day 90 compared with placebo (OR, 0.66; 95% CI, 0.44–0.98). Moreover, no differences in the primary outcome at 90 days were noted when baseline hematoma volume was < 30 mL or > 60 mL.

Currently available data indicate that the greatest risk for hematoma expansion after spontaneous ICH occurs within the first few hours after symptom onset, although approximately one-third of patients will have hematoma expansion at some point after hospital admission.⁴⁸ Identifying patients at the highest risk for hematoma expansion represents a targeted patient population that may benefit from administration of TXA. One proposed biomarker for hematoma expansion is the spot sign on CT angiography or contrast-enhanced CT, which is presumed to represent an active leak of contrast-enhanced blood into the area of the hematoma. The Spot Sign and Tranexamic Acid on Preventing ICH Growth-AUstralasia study (STOP-AUST) was a double-blind, randomized, phase 2 trial completed in 13 stroke centers in 3 countries that compared outcomes of adult patients with spontaneous ICH treated with TXA or matching placebo who had contrast extravasation on CT angiography (ie, positive spot sign) within 4.5 hours of symptom onset and 1 hour of CT angiography.⁴⁹ There were no differences in the primary outcome, which was the incidence of hematoma expansion (increase of hemorrhage volume $> 33\%$ or absolute increase of 6 mL) between the TXA and placebo groups (44% vs 52%, respectively; OR, 0.72; 95% CI, 0.32–1.59; $P = 0.41$). Secondary outcomes including mRS at 90 days, death within 90 days, and thromboembolic events were similar between the TXA and placebo groups. The Tranexamic Acid for Acute Intracerebral Haemorrhage Growth Based on Imaging Assessment (TRAIGE) trial had a similar study design compared to the STOP-AUST trial but enrolled patients up to 8 hours after symptom onset and included patients with blend (seen as a blending of hypo- and hyperattenuating areas with clear

margins within the hematoma) or black hole (a circular hypoattenuating area within a hyperattenuating hematoma) sign on non-contrast CT, which both represent potential imaging markers for patients at risk for hematoma expansion.⁵⁰ Similar to the STOP-AUST trial, there were no significant differences in the incidence of hematoma expansion between TXA and placebo groups (40.4% vs 41.5%, respectively; OR, 0.96; 95% CI, 0.52–1.77; $P = 0.89$) or other reported secondary outcomes. Finally, a prespecified subgroup analysis of the TICH-2 trial evaluated whether the presence of a spot sign influenced the efficacy of TXA.⁵¹ Hematoma expansion in patients with a positive spot sign was similar in patients who received TXA and placebo. Similar findings were reported in patients with spot sign negative comparisons, suggesting that the presence or absence of a spot sign did not influence the efficacy of TXA. Taken together, these results indicate that targeted approaches to identify patients with a positive spot sign are unlikely to influence the effectiveness of TXA.

A total of 2 meta-analyses evaluating various surrogate and clinical outcomes in patients with spontaneous ICH have been published recently.^{52,53} Bouillon-Minois et al evaluated ICH-related mortality by combining the results of the TICH, TICH-2, and STOP-AUST trials.⁵² The authors reported that ICH-related mortality was similar between patients who received TXA and placebo (RR, 1.02; 95% CI, 0.86–1.17). Although the results from the TRAIGE trial were not included, it seems unlikely that the conclusions would be different because there were no significant differences in mortality reported in this trial.⁵⁰ Another meta-analysis by Gao et al evaluated hematoma rate and change in hematoma volume from baseline in patients with spontaneous ICH.⁵³ Results from 3 randomized controlled trials were included in the analysis but did not include data from the STOP-AUST or TRAIGE studies. The authors reported that the rate of hematoma expansion (RR, 0.84; 95% CI, 0.74–0.97; $P = 0.02$) was significantly lower in the TXA groups along with a trend in favor of TXA with respect to change in hematoma volume from baseline (mean difference, -0.98 ; 95% CI, -2.02 to 0.06 ; $P = 0.06$). Collectively, these meta-analyses suggest that TXA decreases the rate of hematoma expansion but does not impact mortality rates.

5 | TXA USE IN ANEURYSMAL SAH

Historically, antifibrinolytic therapy for aneurysmal SAH has been extensively studied with initial reports using aminocaproic acid dating back to 1967.⁵⁴ TXA is the most studied antifibrinolytic agent studied for this indication despite US Food and Drug Administration–approved product labeling listing the use of TXA as a contraindication in the setting of SAH because of concerns related to cerebral edema and infarction.⁵⁵ Rebleeding after aneurysmal SAH is thought to be related to dissolution or fibrinolysis of established clot at the site of the ruptured aneurysm. Although > 50 studies on the use of antifibrinolytic therapy in aneurysmal SAH have been studied, the interpretation of early studies is limited by inconsistent therapeutic regimens, duration of treatment, and issues related to poor study design (eg, uncontrolled, open label, and unblinded).

From a historical perspective, a Cochrane Review published in 2013 evaluated randomized trials comparing oral or intravenous antifibrinolytic agents to control in patients with aneurysmal SAH.⁵⁶ The authors identified 10 trials with substantial variation in the daily TXA dose administered (range, 4–9 g) and duration of treatment (range from 72 hours to up to 6 weeks). The rate of rebleeding at the end of the observation period was significantly lower in patients treated with antifibrinolytic agents compared with control (RR, 0.65; 95% CI, 0.44–0.97). However, the benefits of a lower bleeding rate were offset by a higher rate of cerebral ischemia in patients who received antifibrinolytic agents compared with control (RR, 1.41; 95% CI, 1.04–1.91). Poor patient outcomes defined as death, vegetative state, or severe disability based on Glasgow Outcome Scale or mRS were similar between patients who received antifibrinolytics and control as was death attributed to any cause. Despite the lack of improvement in functional outcomes and mortality, the Cochrane Review suggested that limiting treatment duration to <72 hours as done in the randomized controlled trial by Hillman et al may reduce the risk of rebleeding without increasing the risk of delayed ischemic events.⁵⁷ The study by Hillman et al in addition to others demonstrating benefits of early, short-course TXA in different patient populations has prompted additional research in patients with aneurysmal SAH.

The Ultra-Early Tranexamic Acid After Subarachnoid Haemorrhage (ULTRA) trial was a randomized controlled, open-label trial with masked outcome assessment conducted at 8 treatment centers and 16 referring hospitals in the Netherlands. Adult patients with CT-confirmed SAH and symptom onset for <24 hours were randomly assigned to receive either TXA 1 g bolus followed by continuous infusion of 1 g every 8 hours for up to 24 hours or control.⁵⁸ The incidence of good clinical outcome was similar in patients randomly assigned to TXA and control (60% vs 64%, respectively; OR, 0.87; 95% CI, 0.67–1.13). However, patients who received TXA had lower rates of excellent clinical outcomes compared with control (48% vs 56%, respectively; OR, 0.74; 95% CI, 0.57–0.96). No differences in all-cause mortality at 30 days and 6 months or serious adverse events including rebleeding rate, thromboembolic events, or seizures were reported.

A recently published systematic review and meta-analysis compared several clinical outcomes of patients with aneurysmal SAH treated with TXA or placebo.⁵⁹ The authors reported no differences in all-cause mortality between patients who received TXA and placebo or incidence of poor functional outcome. However, the authors did report a significant reduction in the rate of rebleeding in patients treated with TXA compared with placebo (RR, 0.59; 95% CI, 0.43–0.82; $P = 0.001$). The previously cited meta-analysis by Bouillon-Minois et al included an evaluation of patients with aneurysmal SAH and reported that TXA significantly reduced mortality (RR, 0.72; 95% CI, 0.49–0.96).⁵² Variation in study inclusion (and exclusion) and differences in methodology likely explain the discordant results between the 2 meta-analyses. In addition, interpretation of these meta-analyses is difficult for several reasons, including moderate to substantial heterogeneity between studies along with variation in the timing of treatment initiation, treatment duration, and TXA dose.⁶⁰ TXA use in SAH and spontaneous ICH can be reviewed in Table 1.

6 | TXA DOSING AND ADMINISTRATION CONSIDERATIONS

Much of the data surrounding TXA use in the operative setting supports weight-based dosing that has been shown to sufficiently inhibit fibrinolysis and reduce transfusion requirements.^{61,62} However, given the frequent emergent nature of traumatic and non-traumatic head injuries where it may often be difficult to estimate or determine a patient's weight, fixed-dosing strategies are more appealing to streamline therapy, especially in the prehospital setting where minimal dose preparation manipulations are key. In CRASH-2, the dose that was selected (1 g intravenous bolus followed by an infusion of 1 g given over 8 hours), and subsequently carried over in many other prospective studies, was based on trials carried out in surgical patients and was thought to maximize efficacy and safety in both larger (>100 kg) and smaller (<50 kg) patients.¹⁹ However, there is a paucity of literature examining the differences in outcomes in obese versus non-obese patients with fixed-dose TXA in non-operative indications, and major trials did not report differences based on patient weight subgroups. Franz et al sought to address this gap by collecting data on 165 patients who received fixed-dose TXA for non-operative indications ($\approx 20\%$ with trauma listed as bleed type).⁶³ They found that there were no differences in blood product administration or other secondary clinical outcomes between patients <100 kg or ≥ 100 kg who received fixed-dose TXA.⁶³ Taken together, it likely remains appropriate to give fixed-dose TXA for indications other than surgical-related bleeding.

Another consideration regarding TXA use, especially in the prehospital setting, is whether the intramuscular route is feasible and efficacious compared with the intravenous route without compromising safety. Major trials previously discussed in this review all required intravenous administration of TXA, so it remained unclear how the intramuscular route would affect outcomes. Using pharmacokinetic modeling after a single TXA 1 g intravenous dose, a study carried out in 30 trauma patients with bleeding found that the time to reach therapeutic TXA serum concentrations was within 15 minutes after a single intramuscular TXA 1 g injection.⁶⁴ Furthermore, intramuscular TXA was well tolerated in this study, and this group's findings carry important implications regarding the use of TXA in time-sensitive indications such as traumatic and non-traumatic intracranial hemorrhage, especially in settings where advanced treatment options are limited. Further studies, particularly in patients with trauma, should investigate the use of intramuscular TXA especially in the prehospital setting. Furthermore, a bolus-only regimen may also allow greater feasibility in prehospital and military settings, which served as the basis for including a 2 g intravenous bolus-only treatment arm in the study by Rowell et al.²² In this investigation, however, the time to study drug administration from injury and number of infusion-related deviations were similar between all groups. It remains unclear if a bolus-only dosing strategy would amount to differences in any clinical outcomes as neurologic outcomes and mortality were similar between the 3 treatment arms, but this could be an interesting area of future research.

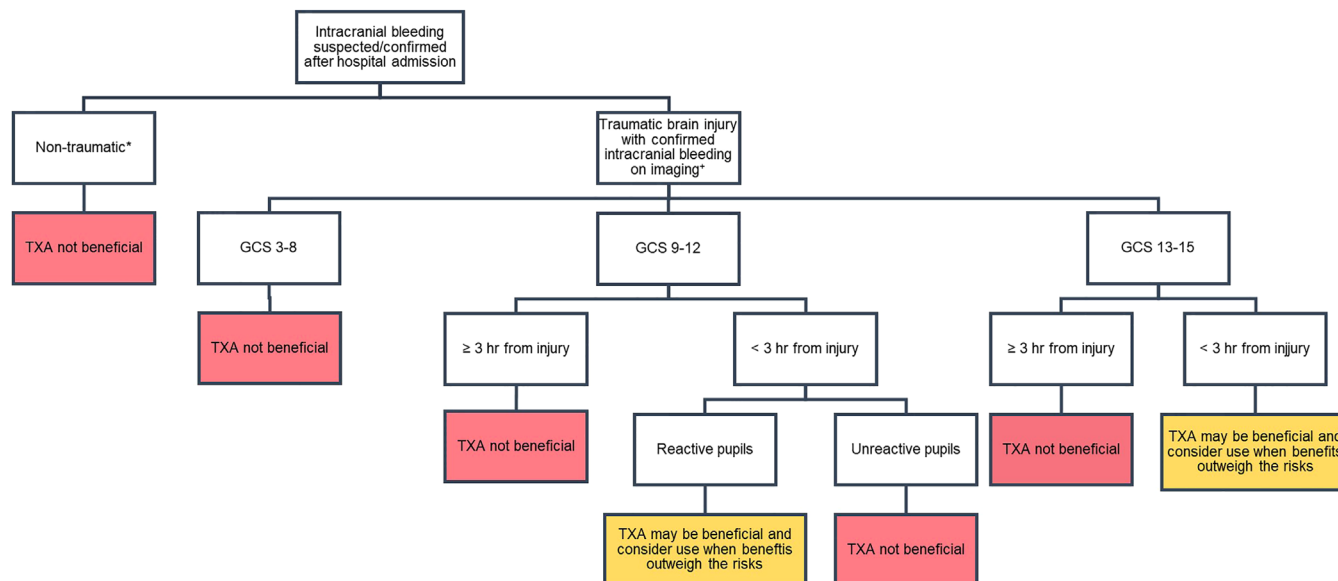


FIGURE 1 Patient assessment pathway after presentation to the hospital for suspected or confirmed intracranial bleeding. *Spontaneous intracerebral hemorrhage or aneurysmal subarachnoid hemorrhage. +Assumes no concomitant extracranial traumatic injuries (ie, polytrauma patients). GCS, Glasgow Coma Scale; TXA, tranexamic acid

7 | CONCLUSIONS AND FUTURE DIRECTIONS FOR RESEARCH

The most important considerations when implementing treatment with TXA in a patient with TBI appear to be severity of injury (eg, baseline GCS score) and setting (hospital vs prehospital). Only patients with mild to moderate TBI (GCS 9–15) had significantly lower mortality rates in the CRASH-3 trial, which remains the largest clinical trial in the setting of TBI and carries the greatest weight in published meta-analyses (88%–94%),^{20,36,37} which raises questions regarding the purported mechanism of TXA that would be expected to result in more benefit in patients with severe injuries and a greater degree of fibrinolysis. Although the CRASH-3 study did not demonstrate benefit in the overall cohort of patients with TBI, improvements in patient outcomes with mild to moderate TBI cannot be completely ignored when the treatment regimen is associated with relatively low rates of serious adverse events. We provide a patient assessment pathway that rationalizes the likelihood of clinical benefits with the use of TXA (Figure 1). Future studies in TBI research will hopefully address the imbalances in patient baseline disease severity, TXA dosing regimens, and reported outcomes that exist with currently available trials.⁶⁵

In patients with spontaneous ICH and aneurysmal SAH, the role of TXA to improve clinical outcomes appears to be minimal. In patients with spontaneous ICH, TXA may reduce the risk of hematoma expansion and change in hematoma volume; however, it does not appear to improve mortality or functional outcomes. Patients who might benefit from TXA treatment include those with a baseline hematoma volume of 30–60 mL and in those receiving a combination of TXA and tight blood pressure control.⁴⁸ However, these findings are hypothesis generating and may represent future research opportunities. In

patients with aneurysmal SAH, a lower risk of rebleeding must be balanced with potential lower likelihood of clinically meaningful functional outcomes, and management of these patients should focus on other non-TXA-related therapies.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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